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Karolinska Institutet, Stockholm, Sweden

# **RECTAL CANCER SURVIVORSHIP – WORK LOSS AND LONG-TERM MORBIDITY**

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Cover art – *Impression, sunrise*, the first impressionism artwork by Claude Monet 1872. It symbolizes the still hazy but promising future of the research on rectal cancer survivorship.

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# Rectal cancer survivorship –work loss and long-term morbidity

## THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To all of those have been afflicted by rectal cancer.



## ABSTRACT

In the last few decades, due to early detection and advances in treatments, rectal cancer survival has been improved significantly. Meanwhile, rectal cancer survivors and health practitioners are facing more challenges arising from the disease, in terms of survivors' long-term morbidity and work ability. The general aims of the register-based doctoral projects therefore include: 1). to evaluate the short- and long-term work loss in incident relapse-free rectal cancer survivors, together with the underlying association between work loss and survivors' clinical characteristics; 2). to investigate the long-term cardiotoxicity in irradiated relapse-free rectal cancer survivors; 3). to systematically estimate the long-term drug use as a proxy for morbidity in relapse-free rectal cancer survivors.

In Study I, we included 2815 curatively treated working-age rectal cancer patients without previous disability pension and their matched general comparators. After a median follow-up of 6 years (range 0-10 years), we found nearly one fourth relapse-free survivors and one tenth of their comparators were on disability pension listing, making the disability pension risk significantly doubled in the relapse-free survivors. Abdominoperineal resection was associated with higher disability pension risk than anterior resection. Surgical complications and reoperation also yielded more risk in survivors' disability pension. In Study II, using the same study design as the previous study, we found the median work loss days during the 1<sup>st</sup> after treatment was 147 days and 336 days among relapse-free rectal cancer survivors without (n=2,529) and with (n=909) prediagnostic work loss history, respectively. Among those who had prediagnostic work loss, the post-treatment work loss varied very little by clinical characteristics; whereas among those without any prediagnostic work loss, advanced stage at diagnosis, operated with Abdominoperineal resection, neoadjuvant (chemo)radiotherapy treatment and surgical complications were all associated with higher work loss risk in survivors.

In Study III, we included 14901 register-based (9227 received preoperative radiotherapy (RT) and surgery and 5674 were treated only with surgery) and 2675 trial-based (randomized into preoperative RT or not followed by surgery) relapse-free rectal cancer patients during a maximum follow-up of 18 and 33 years, respectively. We found no significant overall or subtypes of cardiovascular risk associated with preoperative RT. Although a slightly elevated risk of venous thromboembolism was noted in both cohorts during the first 6 months following treatment, the absolute number of patients affected was rather low, hence the safety of RT was further assured.

In Study IV, we evaluated the detailed prescribed drug dispensing using defined daily doses (DDDs) by the Anatomical Therapeutic Chemical (ATC) classification among relapse-free rectal cancer patients across a maximum follow-up of 10 years. In comparison to the general population, rectal cancer survivors had a slight increase in overall drug use. While the survivors did acquire more drugs in digestive system, this could be due to both the long-term disease complications and potential prophylactic treatment.

# LIST OF SCIENTIFIC PAPERS

- I. **Risk of disability pension in patients following rectal cancer treatment and surgery**  
**Lingjing Chen**, Ingrid Glimelius, Martin Neovius, Sandra Eloranta, Sara Ekberg, Anna Martling, Karin Ekström Smedby  
*Published*  
*British Journal of Surgery* 2015 Oct;102(11):1426-32. doi: 10.1002/bjs.9885
- II. **Work Loss Duration and Predictors Following Rectal Cancer Treatment among Patients with and without Prediagnostic Work Loss**  
**Lingjing Chen**, Ingrid Glimelius, Martin Neovius, Sandra Eloranta, Sara Ekberg, Anna Martling, Karin Ekström Smedby  
*Published*  
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Doi:10.1158/1055-9965.EPI-16-0112
- III. **Short- and long-term risks of cardiovascular disease following radiotherapy in rectal cancer in four randomized controlled trials and a population-based register in Sweden**  
**Lingjing Chen**, Sandra Eloranta, Anna Martling, Ingrid Glimelius, Martin Neovius, Bengt Glimelius, Karin Ekström Smedby  
*Submitted*
- IV. **Long-term use of prescribed drugs in rectal cancer survivors compared to the general population in Sweden**  
**Lingjing Chen**, Sandra Eloranta, Anna Martling, Ingrid Glimelius, Martin Neovius, Karin Ekström Smedby  
*Manuscript*



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## LIST OF ABBREVIATIONS

ACT	Anatomical Therapeutic Chemical
CDR	Cause of Death Register
CI	Confidence interval
CVD	Cardiovascular disease
DDD	Daily defined dose
DVT	Deep vein thrombosis
ESMO	European Society for Medical Oncology
IBD	Inflammatory bowel disease
ICD	International Classification of Diseases
IRR	Incidence rate ratio
LARS	Low anterior resection syndrome
MiDAS	Micro Data for Analysis of the Social Insurance
NPR	National Patient Register
PE	Pulmonary embolism
PDR	Prescribed Drug Register
RCT	Randomized Controlled Trial
RT	Radiotherapy
SCRCR	Swedish Colorectal Cancer Registry
SCREESCO	Screening of Swedish Colons
SEER	Surveillance, Epidemiology and End Results Program
TME	Total Mesorectal Excision
TRP	Total Population Register
VTE	Venous thromboembolism
LISA	Longitudinal Integrated Database for Health Insurance and Labour Market Studies

# 1 BACKGROUND

## 1.1 CLASSIFICATION AND SYMPTOMS OF RECTAL CANCER

The rectum is at the lowest part of the large intestine and is located within the pelvis. By rigid sigmoidoscopy, the rectum counts between 10cm and 15cm from the anal verge (1, 2). The most common symptom of rectal cancer is rectal bleeding, followed by defecation disturbance and abdominal pain (3). Many patients also experience intestinal obstruction (3).

## 1.2 INCIDENCE, RISK FACTORS AND SURVIVAL OF RECTAL CANCER

Cancer in the rectum constitutes one third of all colorectal cancer cases, which in turn is the third most common cancer group in the world. Colorectal cancer accounts for approximately 10% of all new cancer cases globally (4). The annual number of new rectal cancer cases is around 2000 in Sweden (5). In 2016, the reported number of new rectal cancer cases was 2180 according to the Swedish Colorectal Cancer Register (SCRCR) (5).

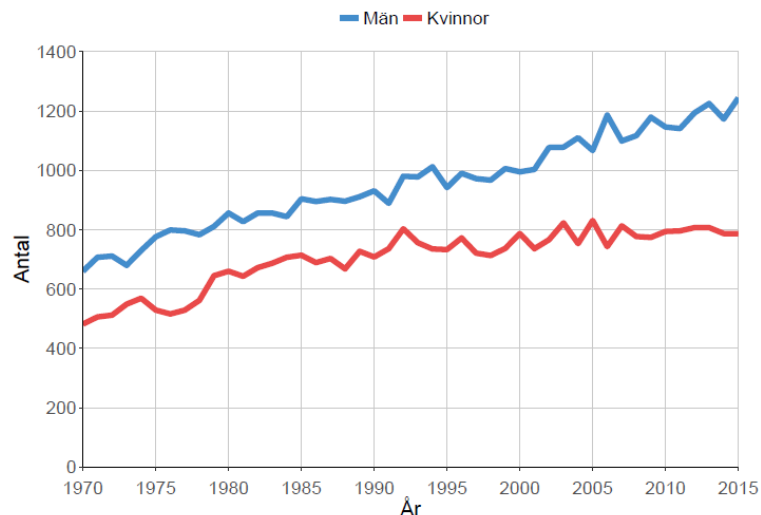


Figure 1. The total number of rectal cancer cases by gender in Sweden, 1970-2015 (5)

Advanced age, being a male and polyps in the colon/rectum are important known risk factors for rectal cancer (6, 7). Further, family history of colorectal cancer also increases the risk of rectal cancer (7). A personal history of inflammatory bowel disease (IBD) could cause dysplasia in the lining of rectum cells which later might increase the risk of rectal cancer (8). Among men, obesity has been associated with higher risk of rectal cancer, whereas an association is more uncertain among women (9). Other life style factors such as physical inactivity, excessive intake of red and/or processed meat, smoking and moderate and/or heavy alcohol consumption has been associated with colorectal cancer risk, but if an association exists specifically also with rectal cancer is unclear (10).

Population screening through colonoscopy can help with removal of polyps before potential cancer development, whereas in Sweden a nationwide population-based screening program for rectal cancer is still under discussion (11). A national study for colorectal cancer

screening, namely SCREESCO (Screening of Swedish Colons), examining the benefits of nationwide screening was first started in February 2014 and will include all study participants until 2019 (11-13). Meanwhile, people between the age of 60 and 69 are invited to colorectal cancer screening by the Stockholm County Council in Stockholm-Gotland region for a screening program using biennial faecal occult blood tests (11, 14).

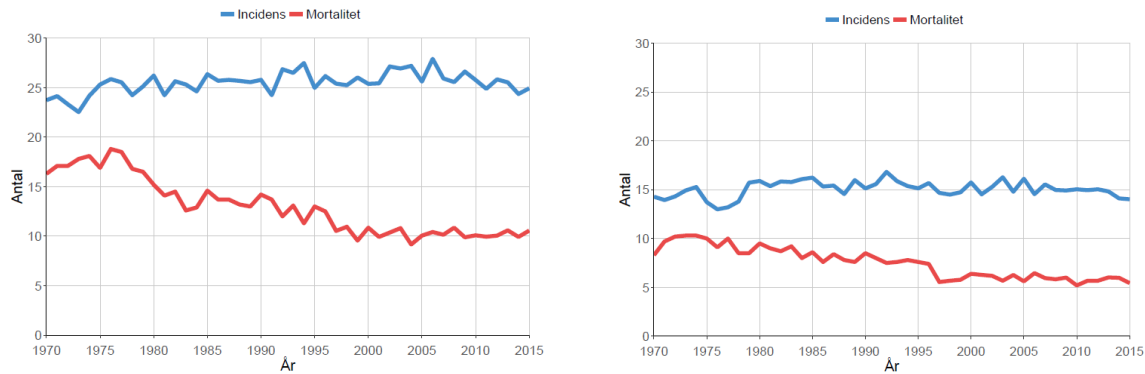


Figure 2. Age-standardized rectal cancer incidence and mortality per 100,000 residents among men (left) and women (right) in Sweden 1970-2015 (5)

Due to early detection and improvements in the treatment of rectal cancer, survival rates in rectal cancer patients have been increasing through the years. In the US, as reported by the Surveillance, Epidemiology and End Results Program (SEER), 5-year relative survival of rectal cancer of all races has risen from 48% during 1975-1977 to 68% during 2005-2011 (15). In terms of stage at diagnosis, the 5-year relative survival varied from 88% for patients with localized disease to 70% for regional and 13% for distant disease in the same material (15). In Sweden, the 5-year relative survival was approximately 95%, 85% and 70% for patients in stage I, II and III disease during 2010-2016 (5) (Figure 3).

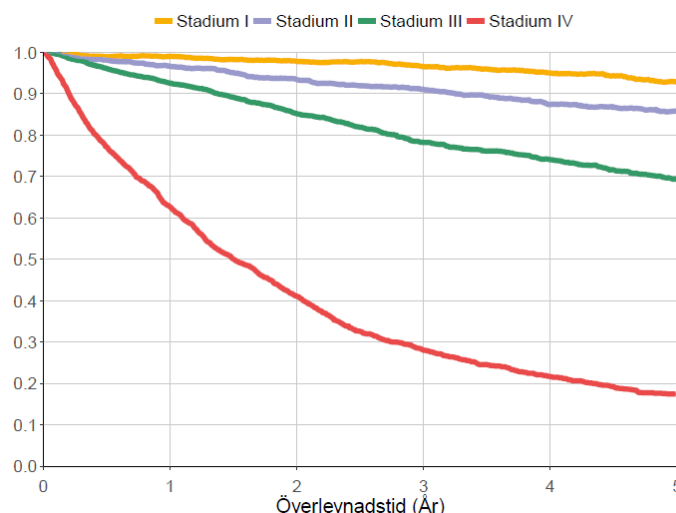


Figure 3. Five-year relative survival by stage in rectal cancer patients diagnosed 2010-2016 in Sweden (5)

### 1.3 TREATMENT FOR RECTAL CANCER

Rectal cancer treatment is based mainly on the cancer stage, in order to remove the rectal tumor completely. Surgery is the most essential part in the treatment regimens, while

radiotherapy (RT), chemotherapy (CT) and chemoradiotherapy (CRT) are often used before or after surgery to achieve lower risk of local recurrence and long-term survival (16-24).

### **1.3.1 The classification of rectal cancers by treatment options**

According to the clinical guidelines from the European Society for Medical Oncology (ESMO), specific treatment strategies are suggested (25). Rectal cancer patients are divided into three groups based on their risk of future local recurrence (or “T4 non-resectable”) – these are early, intermediate and locally advanced, or in other words “good”, “bad” and “ugly” groups (26).

“Good” – patients with early tumors whose risk of local recurrence is very low and who should be treated without pre-treatment.

“Bad” – patients with intermediate risk of local recurrence. These patients are recommended to be treated with preoperative RT followed by immediate surgery.

“Ugly” – patients with the highest risk to fail locally. The recommended treatments for these patients often include preoperative RT and/or CRT (to achieve down-staging) with a delay surgery.

### **1.3.2 Surgery**

Surgery is the most essential part in the treatment of rectal cancer. The choice of surgical procedure depends on tumor size, extent and distance from the anus, alongside with patient’s age, comorbidity and sphincter function. There are mostly three types of curative surgical techniques: 1) anterior resection without anastomosis (Hartmann’s procedure); 2) anterior resection with anastomosis, with or without a colonic reservoir (anterior resection, AR); 3) rectal excision with permanent colostomy (abdominoperineal resection, APR) (17). Total mesorectal excision (TME), which indicates an excision of the entire mesorectal fat, including all lymph nodes is now gold standard in rectal cancer surgery (27). Laparoscopic surgery has been introduced in recent years, and has been associated with similar rates of locoregional recurrence, disease-free and overall survival as open surgery (28).

Comprehensive treatment schedules including preoperative RT or preoperative CRT followed by TME have been associated with further reductions in local recurrence rates and constitute standard treatment in Sweden (17, 27).

### **1.3.3 Preoperative radiotherapy and other oncological treatments**

RT is mostly given before surgery in Europe rather than post-surgery as in the U.S. The addition of preoperative RT to surgery has been shown to reduce local recurrence and possibly also increase overall survival (23, 29-33). Preoperative RT could be given either as short-course of 5Gy/fraction during 1 week (25Gy in total) or as 1.8-2Gy/fraction during 5-6 weeks (45-50.4 Gy in total). The short-course RT and surgery within the following week has been the standard procedure in Sweden and other northern and western European countries, while the long-course RT in combination with chemotherapy (CT) used in most of other

countries (34). The 3-year local recurrence, relapse-free and overall survival have been shown to be statistically similar between the short-course and long-course preoperative RT (35). Previously a Swedish study has suggested that women received significantly less preoperative RT than men (36). Considering the adverse long-term impact from surgery, a “watch-and-wait” approach in rectal cancer management has also been suggested in recent years. This approach favours no immediate surgery in selected patients with complete clinical response after preoperative CRT, avoiding postoperative morbidity and dysfunctions following radical surgery (37, 38).

## **1.4 WORK LOSS RISK AND DETERMINANTS FOLLOWING RECTAL CANCER TREATMENT**

### **1.4.1 Concepts of work disability**

Work disability has been defined as a declared work incapacity associated with a health problem (39). Policyholders and employers have generally financed public and private insurance systems to address the financial consequences of work disability for workers (40). Sickness absence to be absent from work due to sickness reasons, which is characterized by adhering to norms of health behavior, whereas absenteeism is characterized by breaking standard social norms but without direct sanctions (41). In the work loss studies included in the doctoral projects, we used the term sick leave as sickness absence which implies the short-term leave from work, while using disability pension as the long-term and saturated form of leave from work. Both of sick leave and disability pension are covered and compensated by the Swedish social welfare system (see more in Section 3 - Materials and Methods).

### **1.4.2 Short- and long-term work loss risk**

Previous studies have shown decreased work ability among working-age cancer patients (42-49). However, studies of work loss specifically among rectal cancer patients are scarce. Previous studies have often grouped rectal cancer patients together with other cancer patients (43, 45, 49) or with colon cancer patients (44, 50). Among these, studies reporting separate results for rectal cancer patients have suggested that most working-age rectal cancer patients return to work (44, 49), although an increased risk of work loss has been noted compared with general population, including increased risks for both sick leave and disability pension. In a Swedish register-based study encompassing 161 patients, the odds ratio of sickness absence at one year after diagnosis among rectal cancer patients was 1.69 (95% CI: 1.32-2.05) compared to individuals without cancer (49). At the 5<sup>th</sup> year after diagnosis, the odds ratio of having sick leave more than 15 days among 59 rectal cancer survivors was 1.93 (95% CI: 1.10-3.37) compared to matched rectal cancer free individuals (43). In a 10-year perspective, while the risk of sick leave among rectal cancer patients decreased, they in turn experienced higher disability pension compared to the general population (50). In general, previous studies have had limited follow-up of the patients, and have not accounted for the

likely impact of cancer relapse, nor have they investigated clinical and therapeutic determinants to any large extent.

## **1.5 ADVERSE EFFECTS IN RECTAL CANCER PATIENTS AFTER TREATMENT**

### **1.5.1 Adverse effects in general**

Long-lasting treatment complications and a lowered self-reported health condition and quality of life may trouble rectal cancer survivors in comparison to the general population (51-56). Treatment-induced long-term side effects that have been reported include bowel dysfunction, oxliplatin-induced peripheral neuropathy, and pelvic insufficiency fractures after radiotherapy (57, 58). All the potential adverse effects from rectal cancer disease and treatment have led to the reported worse quality of life among rectal cancer survivors (57, 59-67).

### **1.5.2 Cardiovascular disease (CVD) morbidity and mortality related to RT**

A potentially increased risk of CVD overall and especially venous thromboembolism (VTE) has been reported to be associated with preoperative radiotherapy in rectal cancer patients in studies based on several Swedish randomized controlled trials (RCTs). For example, patients treated with RT were reported to have an increased CVD risk based on the Stockholm I and II trials by Pollack et al. (54). Similarly, an increased CVD risk was found during the first 6 months after rectal cancer treatment in the Swedish Rectal Cancer Trial by Birgisson et al. (52). Holm et al also found an increased risk of CVD-related causes of death 60 days within surgery among irradiated rectal cancer patients in comparison to those who were not irradiated in the Stockholm I and II trials (68). CVD-associated death was the main reason of intercurrent death among the irradiated patients, found by Martling et al. based on the Stockholm II trial (31).

Radiation renders acute vascular endothelial damage in rectal cancer patients, which could be the potential reason for the increased VTE risk (69). Furthermore, radiation-induced chronic inflammation which is similar to atherosclerosis could lead to the activation of the transcription factor nuclear factor kappa-B (NF- $\kappa$ B), which could be another potential reason for an elevated VTE risk (70, 71).

### **1.5.3 Digestive system**

Rectal cancer survivors have reported higher risks of experiencing symptoms from the digestive system in quality of life studies (57, 61, 62, 65, 66, 72). A large proportion of the severe bowel dysfunctions including fecal urgency, incontinence, bowel fragmentation and frequent bowel movements are usually resulted from the low anterior resection syndrome (LARS) due to the surgery of low anterior resection (72, 73).

#### **1.5.4 Nervous system**

Mental health and symptoms from the nervous system has always been a concern in long-term rectal cancer survivors (64, 74, 75). Reportedly a significant number of rectal cancer survivors have either clinically meaningful levels of depressive symptoms and anxiety or decreased mental well-being during the course of the disease and recovery (64). Long-term lowered emotional and cognitive functioning, together with fatigue and insomnia have also been suggested to be among these survivors (62). Significantly reduced social well-being have also been observed among patients with ostomy, especially among those who are female or younger than 75 years old at surgery (60).



## **2 AIMS AND RESEARCH QUESTIONS**

1. To assess long-term risk of disability pension among working-age rectal cancer patients, eligible for curative treatment, and its association with clinical and demographic covariates, including relapse, cancer stage, surgical procedures, oncological treatment, education level and unemployment. (Paper I)
2. To estimate short-term work loss rates (up to 5 years) among working-age rectal cancer patients eligible for curative treatment. Specifically, our aim was to study the timing and influence of clinical and demographic variables on work loss, with a particular focus on the impact of work loss history. (Paper II)
3. To investigate risk and timing of cardiovascular morbidity and other vascular complications associated with the addition of RT to surgical treatment (with curative intent) of rectal cancer during short- and long-term follow-up. (Paper III)
4. To study the long-term drug use among rectal cancer survivors by comparing it to the drug use of their general comparators. (Paper IV)

### 3 MATERIALS AND METHODS

#### 3.1 RESEARCH SETTING

All of the studies included in this doctoral thesis are based on Swedish registers, including general health care registers such as the Swedish Cancer Register, the quality-of-care register of colorectal cancer (the Swedish Colorectal Cancer Register), and general population registers such as the Total Population Register. The aim of these registers is to facilitate follow-up, analysis and reporting of population health situations (76). The register data that have been used in the doctoral projects are thus built on the prospective collection of population data. These data are recorded with the unique personal identification numbers which are assigned to all Swedish residents at birth or immigration (76, 77).

#### 3.2 DATA SOURCES

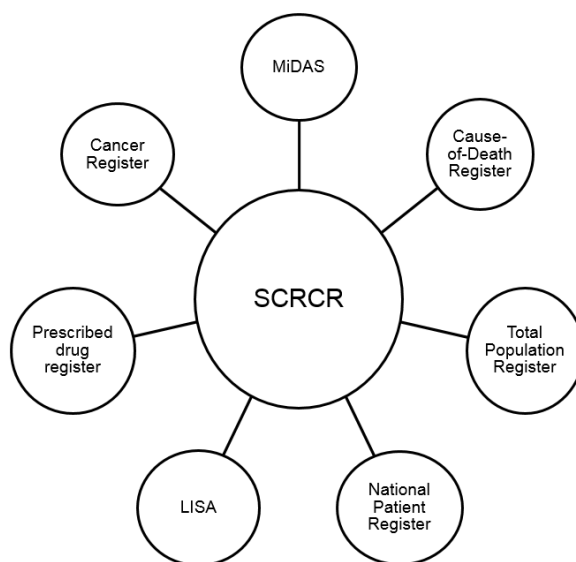


Figure 4. Illustration of the register data sources used in the doctoral projects

#### The Swedish Colorectal Cancer Register (SCRCR)

The SCRCR consists of two parts that report continuously and separately, one is for colon cancer (starting in 2007) and the other for rectal cancer (starting in 1995) (78). The register prospectively includes patients of all ages over the entire country (to six regional oncology centers first and then to one oncology center in the Umeå) (79). The rectal cancer patients included have been diagnosed with invasive adenocarcinoma of the rectum but cases diagnosed at autopsy are excluded (78, 79). Detailed clinical information on preoperative investigations, surgery types, planned and administered oncological treatment, postoperative morbidity (cardiovascular, infectious and/or surgical complications), mortality and reoperation is registered (78, 79). The register is also complemented with continuous follow-up up to 5 years after discharge for all of the patients (79). The quality of the register is high. In 2015, 98.5% of the rectal cancer patients in Sweden were covered by the register (78). In

the same year, the median waiting time from diagnosis to the start of the treatment for these patients was 49 days (78).

### **Micro Data for Analysis of the Social Insurance (MiDAS)**

Micro Data for Analysis of the Social Insurance (MiDAS) database is kept by the Swedish Social Insurance Agency (Försäkringskassan) and records work compensation, including sick leave and disability pension since 1994 (80). The Swedish health care system is tax-funded and offers universal access. MiDAS records single sick leave periods longer than 14 days (single shorter episodes are paid by the employers and thus not registered (except for between January 1997 and March 1998 when 28 days was the limit)). Shorter sick leave episodes (regardless of length) occurs within 5 days of a previous episode are also captured by the MiDAS database (81). Disability pension is registered from day 1 and can be granted to 25%, 50%, 75% or 100%. Those who are registered as unemployed are also entitled to sickness absence compensations.

### **The Swedish National Patient Register (NPR)**

The Swedish National Board of Health and Welfare keeps the NPR. All inpatient care in the country has been recorded in the register ever since 1987. Moreover, the outpatient care provided by public or private caregivers, except within primary health care, has been taken into coverage of the register since 2001. The information included in the register consists of hospital admission and discharge dates, outpatient visit dates and principal- and additional diagnoses made by the treating doctors. The diagnoses were coded according to the International Classification of Diseases 9<sup>th</sup> revision (ICD-9) since 1987 and 10<sup>th</sup> revision (ICD-10) since 1997 (82). According to external validations, the NPR had a coverage of 99% of all the somatic and psychiatric hospital discharges, but the validity behind diagnostic codes may vary (83).

### **The Prescribed Drug Register (PDR)**

The PDR is held by the National Board of Health and Welfare and records all the dispensed prescribed drugs of the whole Swedish population (patient identity missing in 0.3% of all the records) since July 1<sup>st</sup> 2005 (84). The register keeps information on the date of dispensing, amount, substance name and the anatomical therapeutic Chemical (ATC) codes. The ATC classification system consists of 14 main anatomical groups and further therapeutic/pharmacological/chemical subgroups under each main group (85). The ATC codes contains five levels which are anatomical (first), therapeutic (second), therapeutic/pharmacological (third) and chemical (fourth and fifth) levels (85).

### **The Cause of Death Register (CDR)**

This register was first founded in 1961 and contains information on the date and cause of death of all Swedish residents with annual updates (86). The coverage of death and its date recorded in the register is high (86), although the validity of cause of death may be

questionable still (87). Nevertheless, in our projects only the death (yes/no) and its date was considered.

### **The National Cancer Register**

This national register which holds the cancer cases in the whole Swedish population was established in 1958 (88). Approximately 50,000 malignant cancer cases are registered in this registry annually, with high coverage. In these doctoral projects, data from this registry were mainly used to access information about previous cancer diagnoses in the rectal cancer patients registered in the SCRCR and primary cancer diagnoses in the comparison groups.

### **The longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA)**

Statistics Sweden maintains the database of LISA together with the Social Insurance Agency since 1990 (89). It holds existing data from the labor market, educational and social sectors for all individuals ( $\geq 16$  years of age) in Sweden (89). It registers with annual updates of all the aforementioned information of the individuals registered in the country on the 31<sup>st</sup> December every year (89). In the present projects, mainly place of residence and highest level of education were accessed.

### **The Total Population Register (TRP)**

This register is kept by the government agency Statistics Sweden. It contains data on the major life events of the Swedish population, including birth, death and marital status, and migration within the country and to and from other countries with daily updates from the Tax Agency (90). We mainly used this register to identify general population comparators and calculated their follow-up time in the doctoral projects.

### **Four historical randomized controlled trials (RCTs)**

As part of Study III, eligible patients ( $n=2675$ ) from four RCTs on preoperative radiotherapy for rectal cancer conducted during the 1980s and 1990s in Sweden were included as a complement to the register data.

**The Stockholm I trial** (1980-1987) included 849 patients (30), of whom 752 from the Stockholm region were included in the present study.

**The Stockholm II Trial** (1987-1993) enrolled 558 patients aged  $\leq 80$  years (of whom 316 were included before February 1990 and also enrolled in the Swedish Rectal Cancer Trial (31)).

**The Swedish Rectal Cancer Trial** (1987-1990) included 1168 patients aged  $\leq 80$  years (91), of whom 1146 were available.

**The Dutch multicentre Total Mesorectal Excision (TME) trial** (1996-1999) included 219 Swedish patients randomized to short-course preoperative RT plus TME or TME alone (32).

### **3.3 STUDY DESIGN**

In Study I, II and IV, a matched cohort study design was used. Based on the available population register data, we performed matching of comparators to patients by important confounding variables such as age, sex, and calendar year. The underlying reason of this was that such matching prevents an association between exposure and the matching factors among the study subjects already at the start of follow-up (92).

In Study III, both a recent register-based cohort and individuals from four historical randomized controlled trials were combined to perform a comprehensive observational study.

Relapse was handled as a time-varying co-variable in all of the four studies. To be specific, all the patients with relapse information were classified as unexposed before their first relapse and then censored when the relapse occurred.

All the statistical analyses in the doctoral projects were performed with SAS version 9.3/9.4 (SAS Institute, Cary, North Carolina, USA) and STATA release 12.0 (StataCorp LP, College Station, Texas, USA).

### **3.4 STUDY I**

#### **Study population**

Rectal cancer patients (without previous disability pension) diagnosed at their working age (18-61 year old) between 1995 and 2009 were identified from SCRCR. Among all of these patients (5058), those who were not eligible for treatment with curative intent (stage IV disease, ineligible for primary surgery; 1395 patients), patients with other previous primary cancer diagnoses (except non-melanoma skin cancer; 210) and those with disability pension already at diagnosis (497 patients) were excluded. Patients treated by local excision only (77) were also excluded. At last, 2815 patients were included in the final patient cohort in the study population.

For the comparator cohort, we sampled randomly (with replacement) from residents in Sweden who were alive and free from rectal cancer and disability pension at the beginning of the year of diagnosis of the patients. The population comparators were matched (1:5) individually to the patients by sex, age, geographical region of residence and education level (13465 in total).

#### **Exposure**

The exposure of the study was having rectal cancer diagnosis and undergoing curative rectal cancer treatments.

#### **Outcome and follow-up**

Being granted with disability pension (at 25, 50, or 100 per cent) was the study outcome. Rectal cancer patients were followed from date of diagnosis to the date of first emigration,

death, retirement (65 years old), end of study (December 31<sup>st</sup>, 2013) or a maximum of 10 years after diagnosis, whichever came first. For the comparator group, follow-up started from the date of diagnosis of the patients whom they were matched to, until all of the aforementioned endpoints and additional diagnosis of rectal cancer.

### **Statistical analyses**

We applied Cox proportional hazards regression to compare DP rates by demographic characteristics between rectal cancer survivors and the general comparators, and to investigate the impact of clinical characteristics on the risk of DP among the rectal cancer patients. Specifically, incidence rate ratios (IRRs) of DP with 95% confidence intervals (CIs) were estimated. We adjusted the models for the matching variables, unemployment (0-1 years before the rectal cancer diagnosis/match year), and previous sick leave (1-2 years before the rectal cancer diagnosis/match year). Schoenfeld residuals obtained from the Cox model were used to evaluate the proportional hazards assumption.

Furthermore, Poisson regression models (adjusted for the same covariates) were applied to estimate the annual IRRs for DP comparing rectal cancer patients who had not yet encountered a relapse to the general population comparators.

To show the absolute DP risks, we additionally estimated survival functions using the Kaplan-Meier method and cause-specific cumulative incidence functions, treating death and retirement as a competing events.

## **3.5 STUDY II**

### **Study population**

Patients diagnosed with rectal cancer in stage I-III between the age of 18-61 old between 1996 and 2009 were identified in SCRCR. Of them, 3438 were treated curatively (with abdominal surgery). Among these patients, 2,529 (74%) and 909 (26%) were without and with prediagnostic work loss respectively.

Five population comparators per patients were planned to be selected randomly (with replacement) from a subset of the TPR who were alive and rectal-cancer free at the diagnosis date of the patients. Furthermore, they were matched to the patients by sex, age, geographic region of residence, calendar period and education level. In total, 17,027 comparators were identified and matched to the patients (a small proportion of the patients did not have all 5 comparators).

### **Exposure**

The exposure of the study was having a rectal cancer diagnosis and undergoing curative rectal cancer treatments (irrespective of history of prediagnostic work loss).

### **Outcome and follow-up**

The primary outcome of this study were the net days of sick leave and disability pension which were used as a proxy for work loss burden. Calculation of net days of work loss was done by multiplying the number of compensated days by the degree of compensation (25, 50, or 100 percent). The dates and extent of sick leave and disability pension were retrieved from the MiDAS.

The end of follow-up for all study population was date of emigration, retirement (65<sup>th</sup> birthday), death or December 31<sup>st</sup>, 2013, whichever came first. For the patients' relapse-free follow-up, additional censoring date was made for the first date of relapse (either local recurrence of distant metastasis).

### **Statistical analyses**

We provided descriptive summaries of work loss, including the mean, median, 25<sup>th</sup> and 75<sup>th</sup> percentiles of work loss days across follow-up for both rectal cancer survivors (by clinical characteristics) and the general population comparators. A negative binomial regression model (93) as used to compare the rate of work loss (i.e., number of sick leave and disability pension days divided by the total time at risk) between patient subgroups. In this model, the total number of work loss days were treated as a count outcome and an offset term representing the individual's person-time time at risk for work loss was included in the model. Adjustment were made for sex, age at diagnosis, diagnosis year, residence region, education level and unemployment.

## **3.6 STUDY III**

### **Study population**

This study used two study populations, one identified in the SCRCR (the register cohort), and another identified by pooling patients who were previously enrolled in the 4 aforementioned RCTs (the RCT cohort).

All rectal cancer patients registered in the SCRCR between the years 1995 and 2009 (n=24,271) were selected initially for the register cohort. Patients diagnosed with stage IV disease or unknown stage (n=7554), not treated with abdominal surgery (n=862), treated with postoperative RT (n=219), with erroneous relapse date (n=12), or who were older than 85 years old at surgery (n=723) were excluded. In total, 14,901 patients remained in the study population.

On the other hand, the study population also consists of a RCT cohort of patients (n=2675) from four historical RCTs that conducted during the 1980s and 1990s in Sweden. The patients included in the study population were mentioned in the last part of Section 3.2 previously.

The same structure of study population was also used in a previous study published by our research team (94).

## **Exposure**

Patients treated with preoperative RT or CRT treatment (RT<sup>+</sup>) followed by surgery were classified as the exposed group. Patients treated with surgery alone (RT<sup>-</sup>) were the considered unexposed.

## **Outcome and follow-up**

The primary outcome of this study was the main diagnoses of first hospital discharge of CVD occurrence after surgery among rectal cancer patients. Specifically, subtypes of CVD included in the CVD diagnoses were coronary heart disease, arrhythmias and heart failure, stroke, peripheral vascular disease, and pulmonary embolism and deep vein thrombosis.

In a sensitivity analyses, main diagnoses of CVD from the outpatient visits during 2001 and 2009 were also part of the outcome.

The first occurred date of first CVD admission, relapse, death, emigration or December 31<sup>st</sup> 2012 was set as the end of follow-up.

The secondary outcome was the multiple CVD admissions during the study follow-up until the date of relapse, death, emigration or December 31<sup>st</sup> 2012, whichever came first.

## **Statistical analyses**

Incidence rate ratios (including 95% CIs) of first CVD occurrence comparing RT<sup>+</sup> and RT<sup>-</sup> patients were estimated in a Cox proportional hazards model. The IRRs were estimated separately for five follow-up periods (0 up to 6 months, 6 months up to 5 years, 5 years up to 10 years, 10 years up to 15 years, and more than 15 years) for first CVD overall, and for specific subtypes of interest.

The analyses were performed for both the register cohort and the pooled RCT cohort.

In the register cohort, adjustment was made for previous CVD, sex, age at diagnosis, calendar period of surgery, stage, education level, and residential region. In the pooled RCT cohort, stratified Cox regression models (stratified by RCT) were estimated to account for potentially different baseline hazards in the four different trials and only further adjusted for previous CVD.

Multiple events of CVD subtypes were incorporated as supplemental analyses by further estimating Andersen-Gill regression models (95).

## **3.7 STUDY IV**

### **Study population**

A total of 13,703 rectal cancer patients diagnosed between July 1<sup>st</sup>, 2005 and December 31<sup>st</sup>, 2012 and registered in the SCRCR were identified. To capture long-term drug use in rectal cancer survivors and potentially cured patients, patients diagnosed at stage IV or unknown



stage (n= 1527), not treated with surgery/abdominal surgery (n= 3902), with erroneous relapse date (n = 1) were excluded, leaving 8273 rectal cancer survivors in the final study population.

As a comparison cohort, 5 individuals from the Swedish population were sampled randomly (with replacement) from the Total Population Register for each patient. The comparators were matched by sex, diagnosis year and age of the rectal cancer patients. In the end, 41,365 comparators were included in the final study population.

## **Exposure**

Rectal cancer diagnosis and its following curative treatment was the exposure of interest.

## **Outcome and follow-up**

The drug use among both the patient and comparator groups based on the measurement of the drug dispensing extracted from the PDR was the outcome of the study. Furthermore, the drug dispensing was classified into 14 main anatomical groups according to the ATC and several sub-category groups were identified further for specific groups of interest. To facilitate detailed comparison, the defined daily dose (DDD) of dispensed drugs were used to evaluate drug consumption by multiplying the number of packages by DDD per package for every dispensed prescription recorded in the PDR.

All rectal cancer survivors were followed up until their date of relapse, emigration, death or December 31<sup>st</sup>, 2015, whichever occurred first. In comparators, the date of rectal cancer diagnosis was used instead of relapse date, while all the other end dates held the same.

## **Statistical analyses**

We calculated the mean DDDs per year of follow-up for drug use overall, drug use per ATC chapters and for some selected subcategories under particular ATC chapters. Furthermore, 4 annual DDD levels (0, 1-180, 181-360, >360) were used to compare the drug use between rectal cancer survivors and the matched general population comparators.

We used a negative binomial regression model to estimate the rate of DDDs for different drug categories. To relax the assumption of a constant rate of DDD use across follow-up, we split each individual's total person-time at risk into two-year time bands and included these time bands into the model. Moreover, an offset term representing person time at risk was incorporated into the model. A robust estimator of the standard error was used to account for the cluster effect of splitting independent data (96). The models were sequentially adjusted for the matching variables, residential region and education level (model 1), and additionally for the Charlson Comorbidity Index score (model 2) to adjust potentially different distributions of comorbidities in the rectal cancer and comparison group, respectively.

## 4 RESULTS

### 4.1 STUDY I

About 23% of the studied rectal cancer patients were diagnosed below the age of 50 years (median age =55 years). The median relapse-free follow-up was 5.7 (range 0-10) years. The percentage of patients and comparators who had at least one episode of sick leave 1-2 years before diagnosis was around 12% in both groups. In the patients, AR was the most common surgical approach (66%) and 56% of the patients received preoperative CRT. Within 5 years of diagnosis, around 25% of the patients experienced relapse.

During relapse-free follow-up up to 10 years after diagnosis, rectal cancer patients had a more than 2-fold elevated risk of disability pension compared with comparators (IRR=2.40, 95%CI 2.17-2.65) (Figure 5). Including relapse, the risk did not change much (IRR=2.59, 95%CI 2.35-2.85). Covariates such as age, sex, education level, employment status or calendar period at diagnosis also modified the risk elevation in patients compared to their comparators. However, previous sick leave conferred an 8-fold increased risk of receiving disability pension among the patients compared to their comparators (IRR=8.30, 95%CI 6.90-9.97).

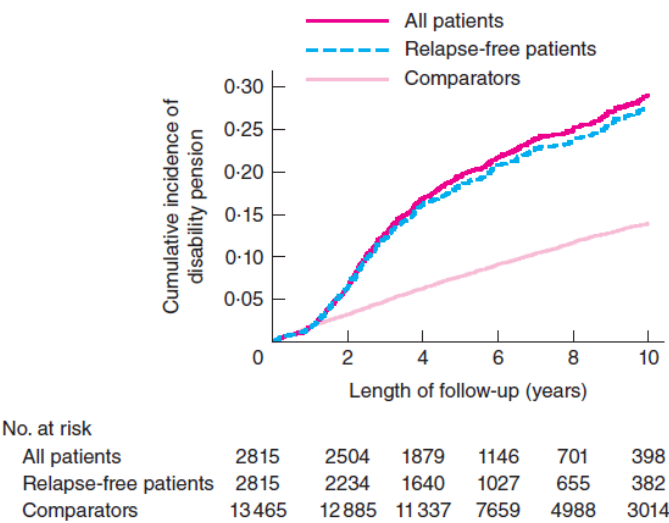


Figure 5. Kaplan-Meier curves showing the cumulative incidence of disability pension in all patients with rectal cancer, relapse-free patients and population comparators.

Regarding clinical determinants of disability pension among rectal cancer patients only, we found that APR was associated with an increased risk of disability pension (IRR=1.44, 95%CI 1.19-1.75) compared with AR. Furthermore, patients who experienced surgical complications or reoperation were also at elevated risk compared with patients with no such complications (IRR=1.33, 95%CI 1.10-1.62 and IRR=1.42, 95%CI 1.09-1.84 respectively).

Table 1. Clinical characteristics among working-age rectal cancer survivors in Sweden.

	Patients with rectal cancer (n = 2815)
Tumour stage	
I	738 (26.2)
II	919 (32.6)
III	1158 (41.1)
Type of operation	
Anterior resection	1875 (66.6)
Abdominoperineal resection	826 (29.3)
Hartmann's procedure	86 (3.1)
Missing	28 (1.0)
Treatment	
Abdominal surgery only	289 (10.3)
Preop. (chemo)radiotherapy	1566 (55.6)
Postop. chemotherapy*	736 (26.1)
Missing	224 (8.0)
Postop. complications (within 30 days)	
Surgical	731 (26.0)
Infectious	174 (6.2)
Other†	215 (7.6)
Reoperation‡	291 (10.3)
Relapse	
Overall relapse	702 (24.9)
Within 5 years	677 (24.0)
Local relapse	147 (5.2)
Within 5 years	139 (4.9)
Distant metastasis	584 (20.7)
Within 5 years	565 (20.1)
Hospital volume	
High	1227 (43.6)
Moderate	604 (21.5)
Low	387 (13.7)
Missing	597 (21.2)

Values in parentheses are percentages. \*Includes postoperative chemotherapy only or in combination with preoperative treatment.

†Includes 45 patients (1.6 per cent) with cardiovascular complication and 170 (6.0 per cent) with other complications. ‡Number of patients having a secondary surgical procedure during the same hospital stay.

## 4.2 STUDY II

A number of 3,438 rectal cancer patients (median age = 56 years of age) were included in the study. Stage III was the main pathological stage at diagnosis in these patients (41%).

Preoperative CRT was the most used oncological treatment (55%) while 63% of the patients had AR as surgery procedure. In total, 2,529 and 909 patients were with and without prediagnostic work loss respectively. Of those who had prediagnostic work loss, the dominant work loss form was sick leave (55%) while the rest (45%) had disability pension. Women, those with lower education level and those diagnosed at advanced age were more likely to have prediagnostic work loss.

During the entire follow-up (median 4 years, range: 0-5 years), the mean work loss days reached its peak during the 1<sup>st</sup> year post diagnosis and then dropped after that. Comparing to patients without prediagnostic work loss, those who had prediagnostic work loss had consistently higher mean levels of work loss days post diagnosis.

Among patients without any previous work loss, 10% of them had no episode of work loss at the 1<sup>st</sup> year after diagnosis and the proportion increased to 74% during the 5<sup>th</sup> year post diagnosis (Figure 6). However, in the patients with previous work loss, the proportion of patients without any work loss was only 30% during the 5<sup>th</sup> year of follow-up.

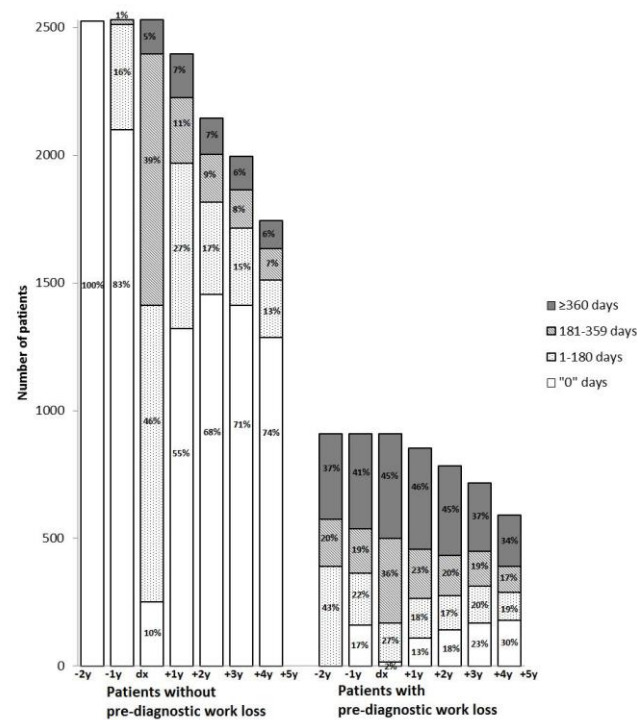


Figure 6. Annual distribution of patients by extent of annual work loss (0, 1-180, 181-359, and >360 days) from 2 years before to 5 years after rectal cancer diagnosis for relapse-free patients without pre-diagnostic work loss before diagnosis (n=2,529) and with pre-diagnostic work loss before diagnosis (n=909).

Post-diagnosis work loss among relapse-free rectal cancer patients without pre-diagnostic work loss was associated varied with clinical characteristics and treatment (Figure 7). Comparing with diagnosis in stage I, being diagnosed in stage II and III were associated with higher levels of mean days of work loss risk 5 years later. APR was associated with higher levels of mean work loss days compared with AR. Postoperative CT also rendered higher levels than preoperative CRT and abdominal surgery alone. Furthermore, patients having surgical complications were more likely to be affected by postdiagnostic work loss than those who had none.

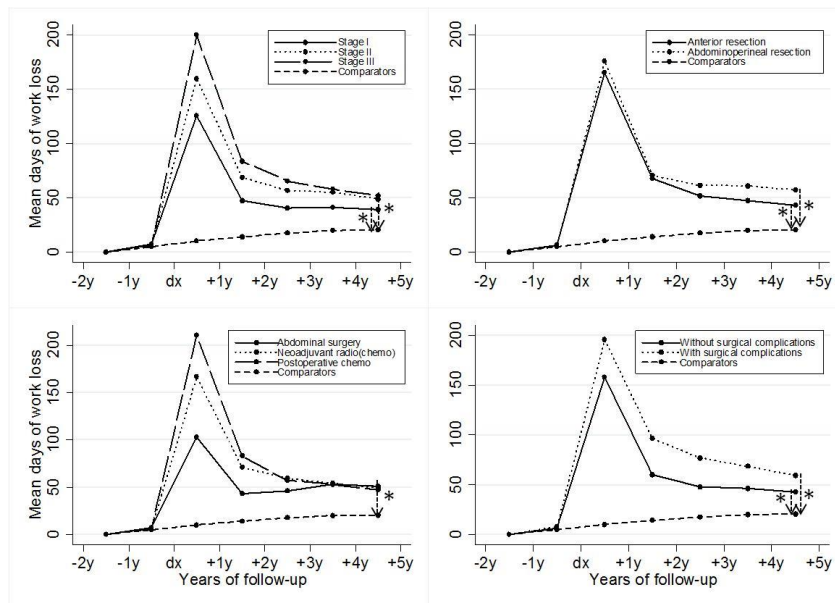


Figure 7. Mean days of work loss stratified by clinical characteristics among relapse-free rectal cancer patients without pre-diagnostic work loss from 2 years before to 5 years after diagnosis. \*p value for the differences of mean days of work loss

between adjuvant chemotherapy – treated patients and comparators is 0.007, and the differences between the other two sub-treatment groups and comparators are both <0.001.

### 4.3 STUDY III

In the final study population, we had the register-based SCRCR cohort of 14,901 rectal cancer patients (62% received preoperative RT and surgery (RT<sup>+</sup> treatment)) and RCT-based cohort of 2,675 rectal cancer patients (49% received RT<sup>+</sup> treatment). All of these patients were diagnosed with stage I-III rectal cancer. Median age was of 70 and 69 years for the SCRCR and RCT cohorts respectively. The median follow-up length of the SCRCR was 6 years and RCT cohort 5 years, whilst the maximum follow-up length was 18 and 33 years for these two cohorts respectively.

In the register-based SCRCR cohort, no association between preoperative RT and the risk of CVD overall in adjusted analyses was found (IRR=0.99, 95%CI 0.92-1.06) (Figure 8). A significantly lower overall CVD risk was found among RT<sup>+</sup> patients 0.5 to <5 years from surgery, but we found no significant relationship between those two during the other follow-up periods. VTE risk increased in RT<sup>+</sup> patients (IRR<sub>overall</sub>=1.41, 95%CI 1.15-1.72) compared to patients treated with RT<sup>-</sup>, mostly in the first 6 months after surgery (IRR<sub>6 months</sub>=2.02, 95%CI 1.43-2.87), with 129 and 50 events found among RT<sup>+</sup> and RT<sup>-</sup> groups, respectively. The risk of deep vein thrombosis (DVT) increased significantly (IRR=2.50, 95%CI 1.57-3.99) during the first 6 months, whereas risk of pulmonary embolism (PE) was not significantly elevated.

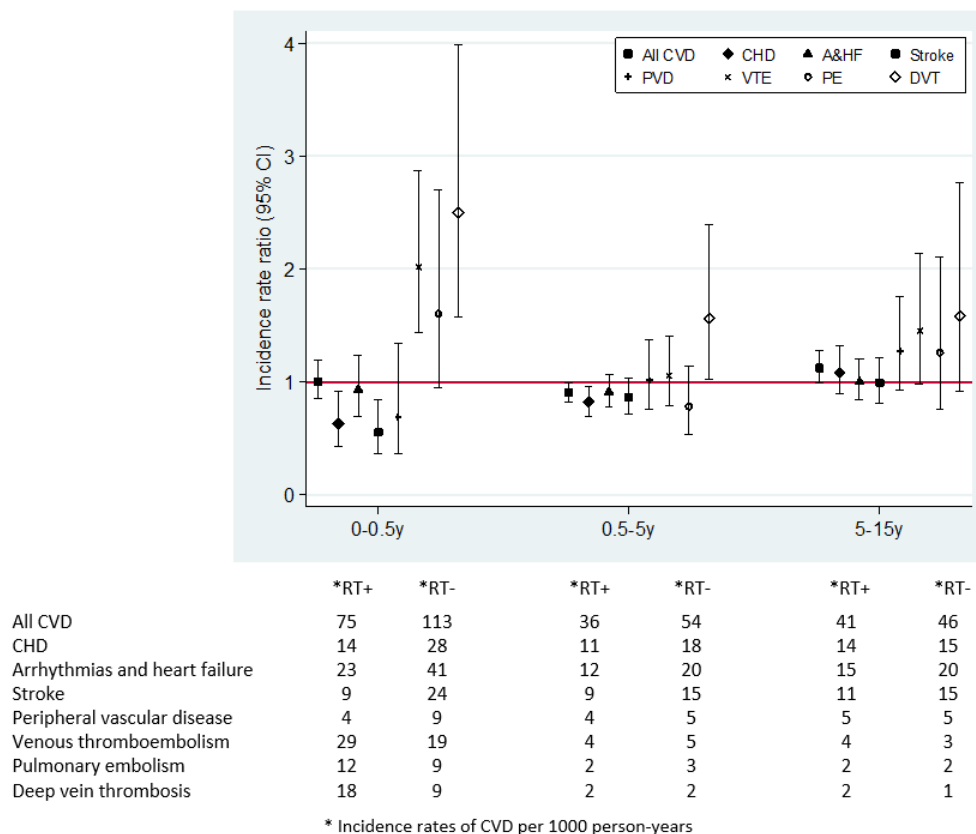


Figure 8. Relative risk of first cardiovascular disease (CVD) events overall and by subtype among relapse-free radiotherapy-treated (RT+) patients compared with patients treated with surgery alone (RT-) in the Swedish Colorectal Cancer Register (SCRCR)

For the RCTs, no increased risk in CVD overall, or any CVD subtypes was found to be related to RT treatment, except for DVT (data not shown).

The absolute number of VTE cases and rates of VTE were shown (Figure 9). The absolute VTE rates reached their peak in the 2<sup>nd</sup> month following treatment. In the RCTs, the general pattern was similar but the absolute numbers were lower (data not shown).

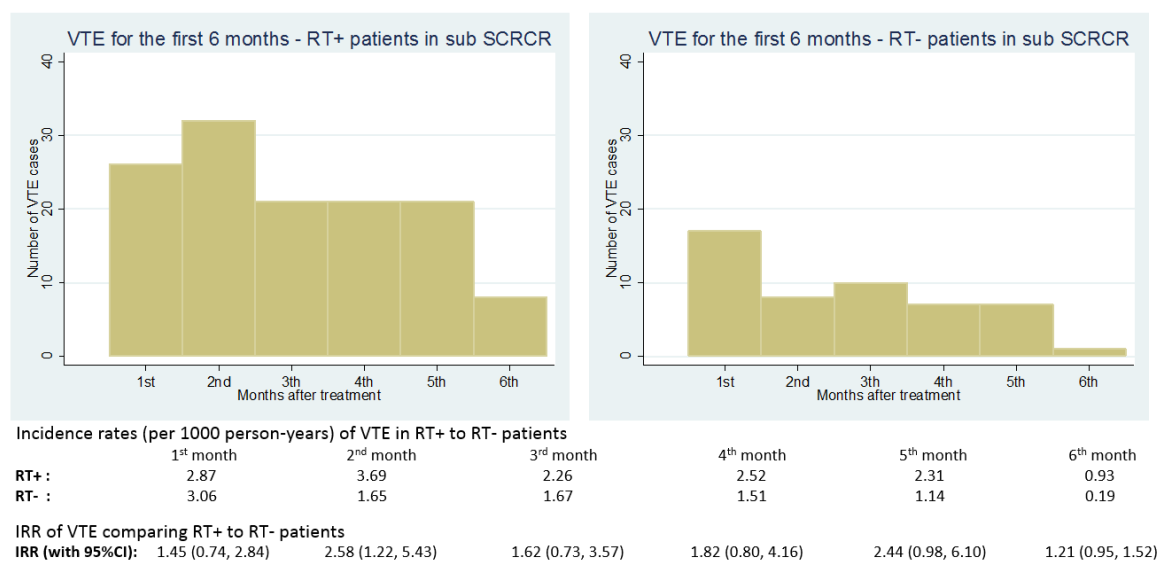


Figure 9. Incidence rates and incidence rate ratio (IRR) of venous thromboembolism (VTE) during the first 6 months following surgery among relapse-free radiotherapy treated (RT+) patients and patients treated with surgery alone (RT-) in the Swedish Colorectal Cancer Register (SCRCR)

#### 4.4 STUDY IV

The median age of the study population was 70 years and the majority were men (60%). Patients and comparators were followed for a median time of 5 (0-10) years and 6 (0-10) years respectively. The distribution of covariates of sex, age and calendar period of surgery/matching was well balanced between the patients and comparators due to matching. The percentage of any kind of comorbidity (CCI>0) occurred in 28% and 29% of patients and comparators respectively. Stage III (39%) was the most commonly diagnosed pathological stage in the patients while anterior resection (53%) was the most prevalent surgical procedure administrated. Relapse occurred in 18% of the patients.

We observed a slightly higher drug dispensing level reflected in mean annual DDDs in the relapse-free rectal cancer survivors compared to their comparators that were followed for 10 years (Figure 10). In the ATC chapters of drugs of the digestive system and blood and blood organs, we further found a higher use of drugs in patients. The most constant increased use across the entire follow-up among patients was observed in the digestive system drugs, which was always above the mean DDD of 200, while the same drug use was always below 200 in the comparators.

In the adjusted analyses for the subcategories of digestive system drug use, we noted that drug use was significantly different for all of the subcategories, except for the drug use in diabetes (Figure 11). Notably, among the drug use for bowel regulating, the medication of constipation was almost 3-times among patients compared to the comparators (IRR=2.87, 95%CI 2.53, 3.26), while other types of bowel regulating drugs were also dispensed at a 3- to 6-fold increased rate among the survivors in comparison to the comparators.

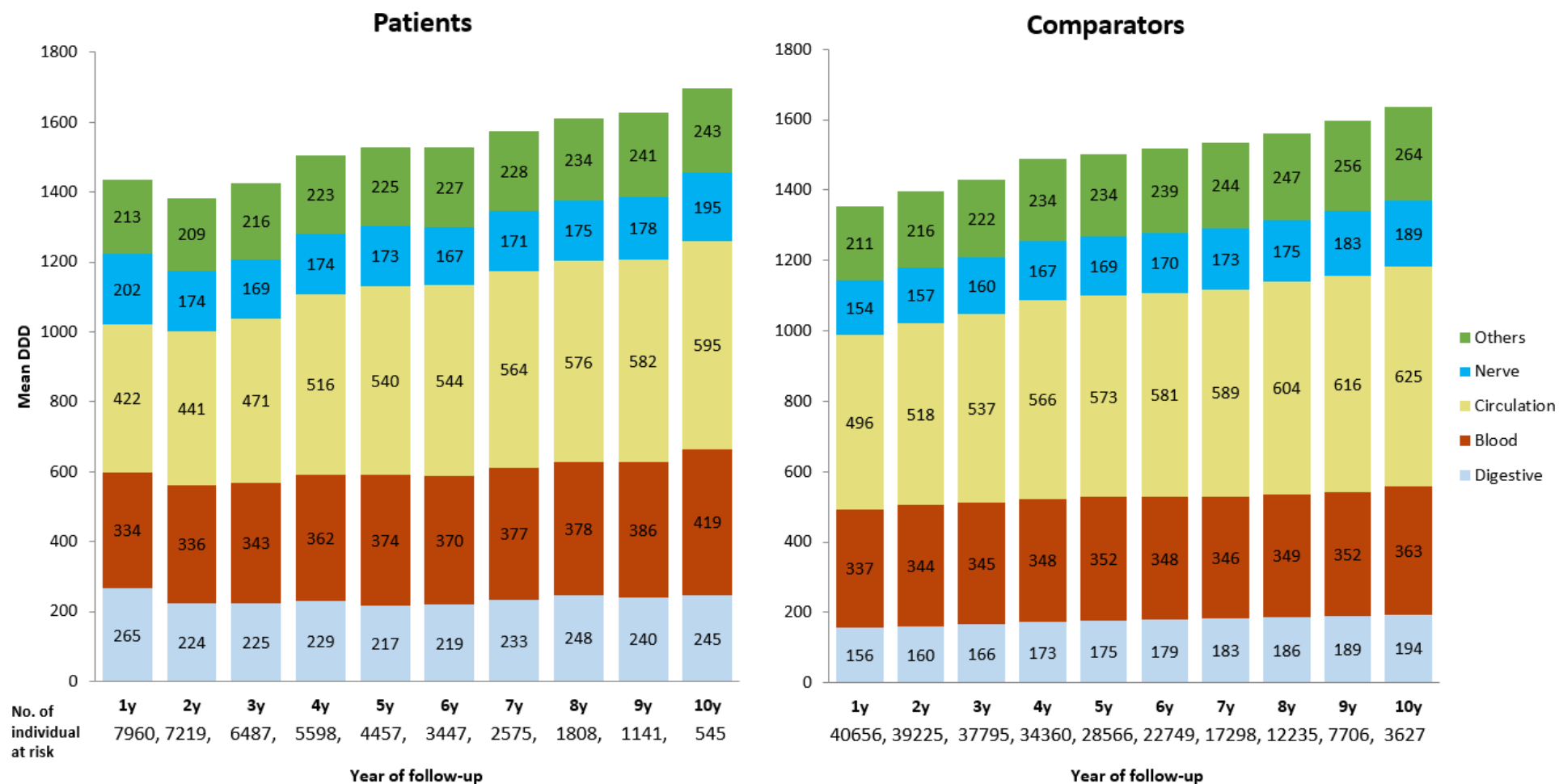


Figure 10. Mean annual defined daily doses (DDDs) of all drug use by broad ATC (anatomical therapeutic chemical classification) categories (digestive, blood, circulation, nerve and other) during 10 years from diagnosis among rectal cancer patients and comparators



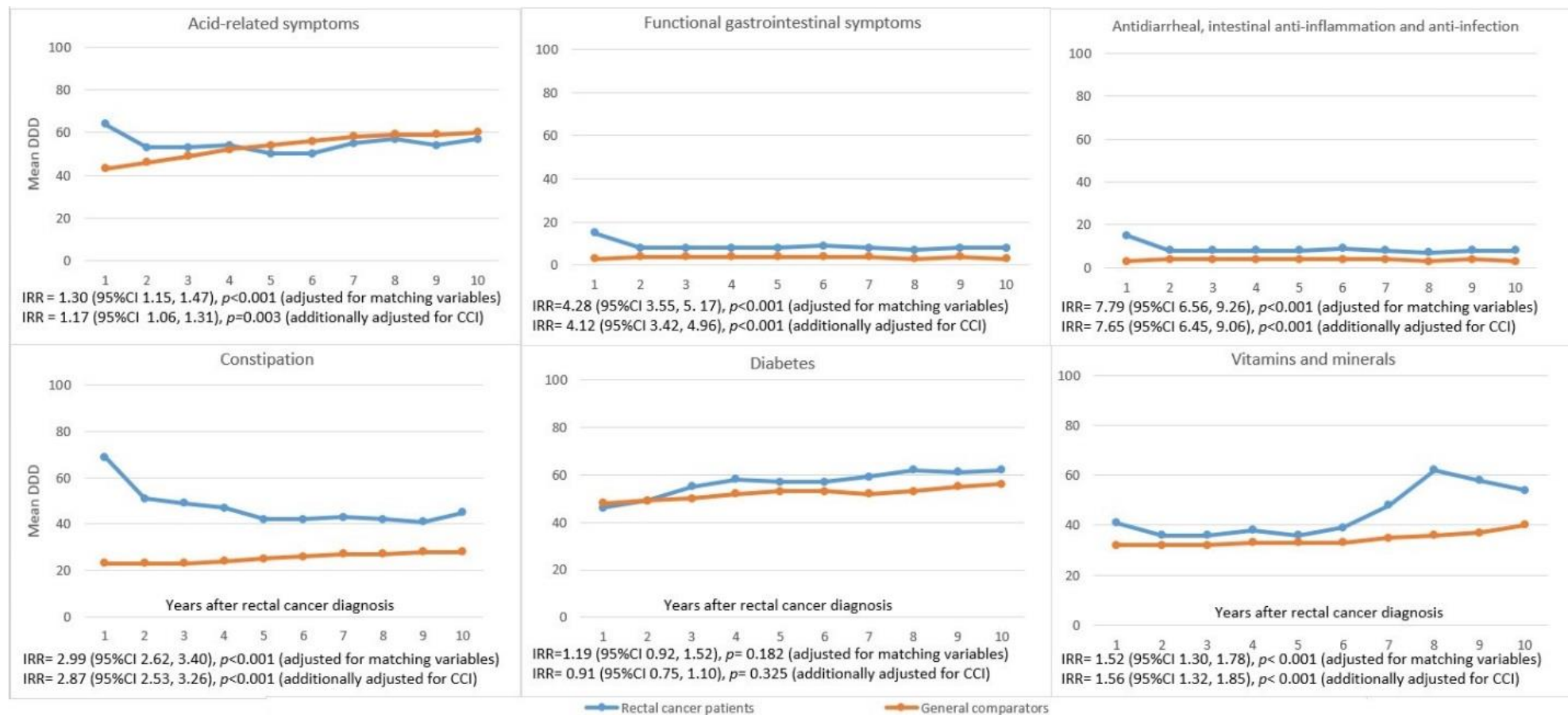


Figure 11. Mean annual defined daily doses (DDDs) of drug use in the digestive system by sub-category during 10 years from diagnosis among rectal cancer patients and comparators

## 5 DISCUSSION

### Short- and long-term work loss in rectal cancer survivors

In Study I and II, we performed two large population-based observational studies to evaluate the burden of work loss (including its short-term form of sick leave and more saturated form of disability pension) following diagnosis and treatment in rectal cancer patients in comparison to randomly sampled comparators from the general population. In the studies, we tried to identify the risk of work loss, the average work loss length in relapse-free rectal cancer survivors, and the demographic and clinical risk factors attributable to the potential risk change.

We came to the conclusion that prediagnostic sick leave could be used as a proxy for prediagnostic comorbidity that can be used to identify the risk groups of patients' future work loss (both sick leave and disability pension) situation. In a shorter perspective, rectal cancer patients without prediagnostic work loss had a median leave from work of 5 months during the 1<sup>st</sup> year after diagnosis, providing clinical guidance as to what can be expected. Furthermore, in our study population of rectal cancer patients, approximately 25% of them had experienced prediagnostic work loss. The majority of these patients tended to be on work leave continuously regardless of their post-diagnostic clinical characteristics. Clinicians should be aware of the patients' early need to occupational rehabilitations, particularly among those with prediagnostic work loss.

The average disability pension risk among the relapse-free rectal cancer survivors was more than 2 times that of the comparators across the entire follow-up of 10 years. Taking the absolute scale, after 10 years from rectal cancer, around 25% of the patients were on disability pension, while the corresponding number for the comparators who received disability pension then was only 10%.

Relapse was shown to be associated with higher rates of work loss in our studies, in terms of both sick leave and disability pension. However, the large bulk of work loss in rectal cancer survivors were not attribute to relapse directly, but was observed among relapse-free patients.

In both the work loss and disability pension studies, we noted that the rectal cancer patients' clinical characteristics were associated with the survivors' work loss situations. Extensive surgery, has been reported to be associated with high morbidity (58). Among abdominal surgeries, the permanent stomas and long-standing side effects after APR were attributed to the higher risk of 5-year work loss and 10-year disability pension comparing to AR. Advanced pathological staging and extensive oncological treatment also had an interplay with survivors' future work absence. Besides, complications particularly surgical complications and the potentially followed reoperation were also associated with significantly elevated risk of taking leaves from work after rectal cancer treatment. Socioeconomic characteristics, specifically lower education level was strongly associated with higher future

work loss in rectal cancer survivors given that the other clinical characteristics held the same in the individuals, which was in line with previous studies (43, 44, 50).

### **Long-term cardiotoxicity following preoperative radiotherapy in rectal cancer survivors**

Previous literature has been inconclusive regarding the cardiotoxicity profile and safety of preoperative radiotherapy treatment used in rectal cancer patients (31, 52, 54, 68, 97), especially in the CVD subtype of VTE. In Study III, we performed an observational study based on both the SCRCR cohort and four RCTs, providing a maximum follow-up of 33 years. With the prolonged study period and large sample size, we confirmed the cardio safety of preoperative radiotherapy in rectal cancer patients with respect to concerns of both overall CVD and CVD subtype risks. Meanwhile, we noted a significantly increased risk of VTE (largely due to DVT) within 6 months after surgery among the patients. However, the affected absolute number of patients was relative small. Therefore, the results do not call for any changes in the general treatment guidelines regarding antithrombotic prophylactic treatment (98).

### **Long-term drug use in rectal cancer survivors**

Drug utilization is studied more and more in the recent years due to the establishment of drug registers. We applied drug use as a proxy for the identification and evaluation of potential long-standing morbidity in rectal cancer survivors for the first time. Long-standing digestive system symptoms including in particular constipation and diarrhea have been shown in quality of life studies previously (61, 65, 66, 72). Our study confirmed that the rectal cancer survivors were at an increased risk to use drugs for the digestive system, particularly bowel movement regulating drugs and drugs used for constipation and diarrhea. Our results partly confirmed the treatment-related symptoms and complications reported previously.

Rectal cancer survivors were also at a higher risk of suffering from mental problems for example depression and anxiety, as previously shown (59, 61-63, 65-67). Based on our current study, we found that considering comorbidities, rectal cancer survivors' psycholeptic dispensing was about one fifth significantly more than the general comparators, while the psychoanaleptics use among the survivors were similar to their comparators. Our findings implied that the survivors tended to be afflicted by insomnia and fatigue rather than depression or anxiety in comparison to the general population.

### **Strengths**

One of the most prominent strengths of the doctoral studies was the use of prospectively recorded population-based health data and comparison cohorts, which had limited the potential biases such as selection bias and misclassification (83, 84, 99, 100). Besides, applying matched cohort study design in Study I, II and IV have helped us to control the confounding influence at baseline by matching the covariates that could cause potential confounding and then adjusting for them in the analyses. Another strength was the long

follow-up that we were able to observe and large sample size we acquired with the help of the register data, both of which contributed to a strong enough statistical power in the studies. Furthermore, clinical characteristics particularly cancer relapse, long-term comorbidity, treatment specifics were made accessible due to the use of mega linkage between different health registers. The potential interactions between survivors' clinical characteristics and outcome variables were also investigated by including the characteristics of interest as interaction terms in the statistical models.

## **Limitations**

One of the weaknesses in the doctoral projects was due to the missing or erroneous relapse information that was reported to be in approximately 10% to 20% of rectal cancer in the SCRCR (101, 102). This incomplete relapse information could have led to the underestimation of relapse impact on the health outcomes to a certain level. The employers rather than the social insurance agency compensated sick leaves shorter than 14 days. Therefore the very early and short-term sick leaves were not included in the projects. Around 3% of the working population (aged 20-64) who voluntarily left the job market was not captured by the work absence compensation and thus not included in our study.

## 6 FUTURE PERSPECTIVES

Based on the results and findings in the current doctoral projects, additional research questions are raised and include:

- What are the specific underlying reasons of work loss among relapse-free rectal cancer survivors?
- How does laparoscopic surgery affect the potential work loss among relapse-free rectal cancer patients?
- Does the watch-and-wait treatment approach for rectal cancer provide relapse-free rectal cancer patients with better prognosis together with less future work loss and higher quality of life situation?
- How does the change in the social system affect the work loss received by the rectal cancer survivors and who are those who are the most affected by the change of system?
- How does the drug dispensing vary among rectal cancer survivors in terms of their demographic and socioeconomic situations?

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